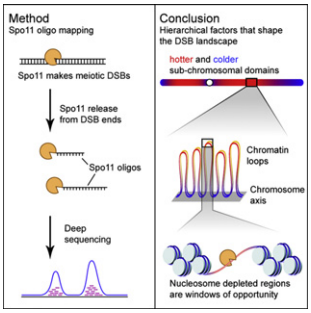
In This Issue

Cell

TLRs Signal Safety for *Salmonella*

PAGE 675

Toll-like receptors (TLRs) are critical for detecting pathogens and then triggering an immune response. Arpaia et al. now find that TLRs are surprisingly required for the survival and replication of *Salmonella typhimurium* in mice. They show that, in the absence of TLRs, bacteria fail to induce virulence genes or to build replicative compartments within the cell. This study suggests that immune signals serve as intracellular contextual cues for certain pathogens, ensuring that their virulence genes are expressed at the right time and place.



Defining Meiotic Breakpoints

PAGE 719

Meiotic recombination relies on DNA double-strand breaks (DSBs) that impact inheritance and genome evolution. Pan et al. now provide a global map of meiotic recombination events with single-nucleotide resolution. This map provides a comprehensive picture of where and why meiotic recombination initiates in yeast, including how chromosomal features shape the recombination landscape. Surprisingly, many recombination events occur outside meiotic hot spots, suggesting that Spo11, the enzyme responsible for generating DSBs, is an opportunistic cutter.

Parkin, PARIS, and PGC-1α

PAGE 689

Parkinson 's disease is often caused by the inactivation of the E3 ubiquitin ligase parkin. Now Shin et al. uncover a new substrate for parkin, named PARIS, which provides a molecular explanation for how parkin inactivation leads to neurodegeneration. PARIS is a transcriptional repressor that accumulates in the brains of Parkinson's disease patients and is required for degeneration of dopamine neurons in mouse models. PARIS blocks expression of PGC-1α and NRF-1, and manipulation of this pathway protects dopamine neurons from degeneration in Parkinson's disease.

New Target for Refractory Breast Cancer

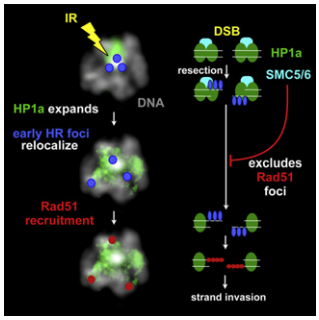
PAGE 703

"Triple-negative" breast cancers are common malignancies with poor prognosis for which no targeted therapeutics exists. Using a genetic screen, Sun et al. now identify the tyrosine phosphatase PTPN12 as a tumor suppressor in triple-negative breast cancers. PTPN12 activity is frequently lost in human tumors, and inhibiting two kinase pathways regulated by PTPN12 (i.e., EGFR/HER2 and PDGFR-β) impairs tumorigenic and metastatic potential of PTPN12-deficient triple breast cancer cells. These findings provide therapeutic inroads to triple-negative breast cancers and reveal a mechanism for activation of proto-oncogenic tyrosine kinases that could be relevant to other cancers.

Stalling Repair until Breaks Move to Safety

PAGE 732

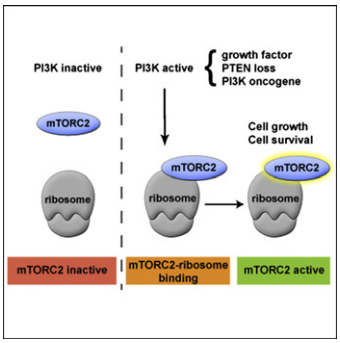
Double-strand breaks in heterochromatin pose a serious threat to genome integrity because their repetitive sequences have increased potential for erroneous exchanges during recombinational repair. Chiolo et al. now discover how heterochromatin overcomes this challenge: heterochromatin proteins postpone strand invasion and final stages of repair until the damaged DNA is moved outside the heterochromatin domain. This spatial and temporal separation of the repair steps prevents aberrant recombination and represents a new mechanism for safeguarding genome integrity.



Elongation Runs on Stress

PAGE 745

Transcriptional attenuation is a regulatory mechanism that prematurely terminates elongation. Now Kim and Levin explain how the Mpk1 MAP kinase in yeast alleviates attenuation to activate the expression of stress-induced genes. Mpk1 blocks recruitment of a termination complex by directly interacting with the elongation factor Paf1C. Moreover, the human homologs ERK5 MAPK and Paf1 can substitute for the yeast factors during this process, suggesting that this MAPK-driven mechanism of transcriptional attenuation is conserved.



mTORC2 Activation by Ribosome Association

PAGE 757

The mammalian target of rapamycin complex 2 (mTORC2) is a highly conserved kinase deregulated in cancer and diabetes, but what activates mTORC2 is unknown. Zinzalla et al. now demonstrate that mTORC2 activates upon association with the ribosome. Insulin stimulates this interaction through PI3K signaling, and the mTORC2-ribosome complex promotes Akt signaling in cancer cells. Together, these results suggest that activation by ribosome association is a conserved mechanism for mTORC2 in cancer and diabetes.

Ubiquitin Only Has Eyes for Lysine 11, Thanks to E2

PAGE 769

Ubiquitin chains linked together at different lysine residues trigger distinct functional consequences in the cell. Wickliffe et al. now determine how the monomeric E2 enzyme Ube2S specifically generates lysine 11-linked ubiquitin chains. A combination of NMR and biochemistry reveals how the Ube2B orients the donor ubiquitin such that the complex transiently recognizes the surface around lysine 11 on the acceptor ubiquitin, but not around ubiquitin's six other lysines. This fleeting interaction creates a competent active site, indicating that that specific chain topology is achieved through substrate-assisted catalysis.

Yap-ing about Crowd Control for Stem Cells

PAGE 782

Proliferation of tissue-specific stem cells is tightly controlled to produce organs of a predetermined size. Schlegelmilch et al. now demonstrate that Yap1, the transcriptional effector of the Hippo-signaling pathway, is a critical modulator of epidermal stem cell proliferation. They find that α-catenin, which has been implicated in sensing cell density, negatively regulates Yap1's nuclear translocation by modulating its interactions with 14-3-3 and the PP2A phosphatase. These findings provide insights into the molecular circuitry mediating "crowd control" in mammalian skin.

Boning Up on Male Fertility

PAGE 796

Not just a simple scaffold, bone is now recognized as an endocrine organ regulating energy homeostasis. Here Oury et al. show that bone also plays a surprising role in regulating male fertility. They find that bone osteoblasts secrete the hormone osteocalcin, which stimulates testosterone production in testicular Leydig cells by binding the receptor Gprc6a.

Astrocytes Feed Memories

PAGE 810

Astrocytes are known primarily for their supportive functions in the central nervous system. Now Suzuki et al. show that astrocytes play an active role in long-term plasticity and long-term memory in rats. Astrocytes in the rat hippocampus generate extracellular lactate during a memory task, and disrupting the lactate transporters on either neurons or astrocytes causes amnesia. These findings suggest that a metabolic coupling between astrocytes and neurons is critical for long-term memory formation.